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ORIGINAL ARTICLE

Prevalence of extended treatment in pulmonary tuberculosis patients receiving first-line therapy and its association with recurrent tuberculosis in Beijing, China

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Background: In China, it is known that extended treatment is given to patients with pulmonary TB after they have successfully completed 6 months of first-line treatment. This practice is not officially reported to the National Tuberculosis Control Programme, so there are no data on its prevalence, its possible benefits in terms of preventing recurrent disease or the costs. This study aimed to provide information, from a single TB dispensary in Beijing, China, on the prevalence of extended anti-TB treatment and its relationship with recurrent TB.

Methods: Retrospective cohort study using the electronic national TB information system and dispensary medical records.

Results: Of 935 patients with pulmonary TB who completed 6–7 months of first-line drug treatment, 399 (43%) were given extended treatment. This was more common in patients with smear-positive disease, and those with lung cavities and more extensive radiographic lobar involvement at the time of diagnosis. Over 3–4 years' follow-up, recurrent disease was not significantly different in patients who received extended treatment (2.8%, 11/399) as compared to those who received the standard 6-month treatment (3.7%, 20/534). The median length of extended treatment was 89 days at a median cost of US$111 for drugs and US$32 for laboratory examinations.

Conclusions: This study shows that extended treatment is common in one TB dispensary in Beijing. Further studies are needed to determine the countrywide prevalence of this practice and ascertain more conclusively the apparent lack of benefit.

Keywords: China, Extended anti-TB treatment, Operational research, Patient costs, Pulmonary tuberculosis, Recurrent tuberculosis

Introduction

China has a well established and well recognized National Tuberculosis Control Programme (NTP).[1] In 2011, the country notified 999 669 cases of TB to WHO with a treatment success rate of 95% in new smear-positive pulmonary TB (PTB) patients registered in 2010.[2] The NTP recommends a 6-months anti-TB treatment regimen for new PTB patients receiving first-line therapy (in accordance with recommendations from WHO and the International Union Against Tuberculosis and Lung Disease [The Union]).[3,4] The anti-TB treatment regimen consists of a 2-month intensive phase with four drugs (isoniazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E]) followed by a 4-month continuation phase with two drugs (RH). These are taken every other day as $2H_3R_3Z_3E_3/4H_3R_3$ or every day as 2HRZE/4HR. If the patient's sputum is smear positive for acid-fast bacilli, the intensive phase is prolonged for 1 month. During treatment, patients are monitored with sputum smear examinations at the start of therapy and at 2, 5 and 6 months, and also with a chest radiograph at the start of therapy and the end of treatment. The anti-TB drugs and necessary examinations are provided free of charge to the patients by the NTP.

In every county of China there is at least one TB special dispensary, which functions as a basic DOTS implementing unit for DOTS (directly observed treatment, short-course). These TB dispensaries are responsible for detecting, diagnosing, registering, treating and supervising most TB patients in their county. The NTP has established a public–public mix system so that all PTB

cases presenting at or treated in public general hospitals are referred to local TB dispensaries.[5]

In some TB dispensaries, or other facilities implementing NTP guidelines, clinicians consider a 6-month treatment regimen to be too short, often on the basis of poor resolution of chest radiograph abnormalities. As a result, some patients are prescribed anti-TB drugs for an additional 2–3 months after completion of 6 months of therapy. Patients have to pay for these medications and for any additional tests that may be carried out. The patients, however, have already been reported as 'cured' or 'treatment completed' on the basis of the 6-month evaluation of sputum smears. Therefore, this extended first-line treatment is not officially documented in NTP reports, and there are no data about the prevalence of such practices, the possible benefits on individual treatment or the prevention of subsequent recurrent disease. Extended treatment may be harmful, in that it increases the economic burden for patients, exposes patients to a longer period on drugs that can have toxic side-effects and creates a risk of drug-resistant TB if there is amplification of single-drug resistance during this extended phase.

Therefore, we conducted an operational research study in a selected TB dispensary to determine the prevalence, duration and cost of extended first-line anti-TB treatment, and to explore if extended treatment was associated with a reduced frequency of recurrent TB.

Methods

Study design

The study had a mixed design, with a descriptive component to determine the prevalence of extended first-line anti-TB treatment and a retrospective cohort component to explore the association of extended treatment with recurrent TB.

Study site and participants (time periods)

The study site was one purposively selected TB dispensary in Beijing, China, which registers almost one-ninth of Beijing city's total TB cases. This dispensary has an excellent medical record system of every TB patient treated since the 1980s.

Study participants were all new PTB patients (smear-positive and smear-negative) registered in the selected TB dispensary from January 2008 to December 2009, and reported as 'cured' or 'treatment completed' after finishing 6 months of treatment.

Smear-negative patients were diagnosed following the NTP guideline,[6] which requires at least three negative sputum smears, radiographic abnormalities consistent with active PTB and exclusion of other disease on the basis of TB history, symptoms and signs, results of immunological or molecular biological examination, and response to anti-inflammatory treatment. 'Cure' was defined as completion of a standard course of combination therapy and successive negative sputum smears during treatment for initially smear-positive patients. 'Completed treatment' was defined as the completion of a standard course without evidence of failure but with no record to show that sputum smear results in the last month of treatment and on at least one previous occasion were negative.

Resources for identifying recurrent TB cases

National TB Information System

A National TB Information System (NTIS) was set up in 2005 to collect information on all registered TB patients in China. It is a web-based electronic data collection and management system. Every TB dispensary has a computer-based system, and relevant information on each registered TB patient is entered within 24 h of diagnosis. This includes all information about TB case-finding and treatment outcomes, and these data are reported into the NTIS. The NTIS also has a direct connection with the Chinese National Infectious Disease Reporting System (NIDRS), a web-based electronic system.[5] If patients come to the general hospital and are suspected or diagnosed as having TB, the doctors are legally obliged to notify this to NIDRS within 24 h (Prevention and Treatment of Infectious Diseases Law, 2004). The NIDRS automatically sends the information to NTIS, informing local TB dispensaries to get in touch with the patient to register them or provide further examinations for final diagnosis. According to a previous survey, only 5.5% of patients with suspected or diagnosed infectious disease in the general hospitals were not notified to NIDRS.[7] These two systems are set up to ensure notification of TB patients if they ever seek help from general hospitals or TB dispensaries.

Recurrent TB cases identified from those systems were diagnosed in different hospitals and TB dispensaries, generally by following NTP guidelines based on sputum smear result.

Data variables and data collection procedures

All eligible patients were identified from the NTIS and were matched with original medical records in the dispensary. These records were then reviewed to collect patients' demographic data and clinical characteristics. To identify those who had received extended treatment, a questionnaire was designed to document the number of days and doses of extended treatment, and details of all examinations done in the extended phase. Unit costs of drug treatments and any examinations were obtained from the dispensary and converted into US$.

TB recurrence was determined by matching patients in the NTIS and NIDRS databases for 2009–2012. The matching was done by uniting personal information through unique identifiers, and if one of the following three conditions were met then this was recorded as a match: 1. the same name, sex and date of birth; 2. the same name, sex, month and year of birth and address; 3. the same name, sex, month and year of birth and confirmation of the information by the patient. In addition, if a patient had a TB recurrence and returned to the same dispensary, these data were recorded and therefore obtained from the medical files.

The data from NTIS and NIDRS were extracted as Excel files and the data from medical records were double entered into EpiData. This was done between March and September 2013.

Analysis and statistics

The proportion of patients who had received extended treatment was ascertained. The baseline characteristics and outcome variables such as recurrent TB were compared between patients with and without extended treatment using the χ^2 test. The median length of extended treatment and the costs of extended treatment were calculated. Levels of significance were set at 5% ($p<0.05$).

Table 1. Demographic and clinical characteristics and treatment success of 935 new patients with pulmonary TB who extended treatment beyond 6 months or received 6 months' standard treatment, Chang Ping TB dispensary, Beijng, China, 2008–2009

Variable	Extended treatment n (%)	Standard treatment n (%)	Total
Sex			
Male	244 (61)	343 (64)	587 (63)
Female	155 (39)	193 (36)	348 (37)
Age (years)			
0–14	0	0	0
15–24	176 (44)	270 (50)	446 (48)
25–34	96 (24)	101 (19)	197 (21)
35–44	59 (15)	66 (13)	125 (13)
45–54	38 (9)	50 (9)	88 (9)
55–64	12 (3)	27 (5)	39 (4)
≥65	18 (5)	22 (4)	40 (4)
Residence			
Local	170 (43)	223 (42)	393 (42)
Non-local	229 (57)	313 (58)	542 (58)
Occupation			
Peasant	133 (33)	182 (34)	315 (34)
Housework	30 (8)	44 (8)	74 (8)
Worker	35 (9)	20 (4)	55 (6)
Student	0	1 (0)	1 (0)
Others	201 (50)	289 (54)	490 (52)
Type of TB			
Smear-positive PTB	91 (23)	46 (9)	137 (15)
Smear-negative PTB	308 (77)	490 (91)	798 (85)
Sputum smear grading			
Scanty smear	0	0	0
1+	23 (6)	15 (3)	38 (4)
2+	27 (7)	10 (2)	37 (4)
3+	19 (5)	12 (2)	31 (3)
4+	22 (6)	9 (2)	31 (3)
Associated extrapulmonary TB			
No extrapulmonary TB	336 (84)	490 (91)	826 (88)
Pleurisy	55 (14)	41 (8)	96 (10)
Extrapulmonary TB	8 (2)	5 (1)	13 (1)
Radiographic cavities			
Present	83 (21)	43 (8)	126 (13)
Absent	316 (79)	489 (91)	805 (86)
Not recorded	0	4 (1)	4 (0)
Involved lung lobes			
0	0	0	0
1	226 (57)	360 (67)	586 (63)
2	119 (30)	135 (25)	254 (27)
3	28 (7)	26 (5)	54 (6)
4	9 (2)	6 (1)	15 (2)
5	17 (4)	9 (2)	26 (3)
Duration of intensive treatment			
Prolonged for 1 month	3 (1)	2 (1)	5 (1)
Not prolonged	396 (99)	534 (99)	930 (99)
Outcome of 6-month treatment[a]			
Cured	91 (23)	44 (8)	135 (14)
Treatment completed	308 (77)	492 (92)	800 (86)
Total	399 (100)	536 (100)	935 (100)

PTB: pulmonary tuberculosis.
[a] Based on 6-month evaluation of sputum smears.

Results

There were 935 eligible patients, of whom 399 (43%) had received extended treatment. Characteristics of the two patient groups, those who extended their treatment and those who took the 6-month standard treatment, are shown in Table 1. There were no significant differences with respect to sex, age group, residence, and whether the intensive phase of treatment was prolonged. However, significant differences were found with respect to occupation (χ^2=11.34, p=0.02), type of TB (χ^2=37.01, p<0.01), associated extrapulmonary TB (χ^2=11.54, p<0.01) and radiographic cavities (χ^2=31.52, p<0.01). The overall relative risk (RR) of receiving extended treatment was 1.72 (95% CI 1.49–2.00) among smear-positive patients compared to smear-negative patients, while RR was 1.68 (95% CI 1.44–1.95) among patients with radiographic cavities compared to patients without. Linear-linear relations were found for sputum smear grading (χ^2=32.17, p<0.01) and the number of lung lobes involved (χ^2=14.85, p<0.01).

Findings with respect to recurrent TB are shown in Table 2. Of the 399 patients whose treatment was extended beyond 6 months, 11 patients (2.8%) developed recurrent TB during the next 3–4 years; of those 11, 4 were sputum smear positive and 7 were smear negative. Of the 536 patients who did not receive extended treatment, 20 (3.7%) developed recurrent TB during the same 3–4 years; of those 20, 9 were sputum smear positive, 7 were smear negative and 3 did not report smear results. There was no significant difference in recurrent TB between these two groups (χ^2=0.68, p=0.41). Nearly half of the recurrent TB occurred in the first year after treatment completion in both groups (5/11, 45.5% and 9/20, 45.0%, respectively).

The regimen, duration and drug costs of extended treatment are shown in Table 3. The overall length of extended treatment was 89 days at a total cost of US$111 for the drugs. In most patients, extended treatment consisted of first-line anti-TB drugs. Patients taking rifampin (R) and isoniazid (H) constituted 41% of all these patients; their median duration of treatment was 71 days at a cost of US$85 per patient for drugs. Another 125 patients (31%) took RH and ethambutol (E) with a median duration of 90 days at a cost of US$123 per patient. Other frequently used regimens were rifapentin (L) and isoniazid (H), LHE and HE, the median durations were 91, 101 and 108 days respectively, and the median cost for drugs was US$86, US$156 and US$191 per patient.

During the extended treatment period, additional examinations were performed the associated costs of which are shown in Table 4. Out of 399 patients who extended treatment, 250 patients (63%) received at least a chest radiograph to determine whether there was radiographic improvement. The median number of times that a chest radiograph was performed was two. Most patients received a routine blood test (272/399, 68%), a routine urine test (250/399, 63%) and tests of hepatic/renal function (274/399, 69%) to monitor adverse drug reactions. Sputum smears were performed again in 18/399 patients (5%) and sputum cultures in 6/399 patients (2%); some patients received other examinations such as blood glucose measurements, B-scan ultrasound examination and sputum cytology examination. In all, 287 patients (72%) received laboratory examinations or tests at a median of eight tests per patient and a cost of US$32 per patient.

Table 2. Recurrent TB: frequency and time of onset among 935 patients seen at Chang Ping TB dispensary, Beijng, China, 2008–2009

Time since completion of TB treatment (years)	Recurrence after extended treatment (N=399) n (%)[a]	Recurrence after standard treatment (N=536) n (%)[a]
<1	5 (1.3)	9 (1.7)
<2	9 (2.3)	14 (2.6)
<4	11 (2.8)	20 (3.7)

[a] n (%) values are cumulative over time.

Discussion

This study is the first of its kind in China to report a rather high prevalence (43%) of extended anti-TB treatment in TB patients.

Table 3. Regimen, duration and drug costs of extended treatment in 399 patients with TB seen at Chang Ping TB dispensary, Beijng, China, 2008–2009

Regimen	Patients n (%)	Median duration of treatment (days) (IQR)	Median drug cost (US$) per patient[a] (IQR)
Rifampin and isoniazid	163 (41)	71 (31–115)	85 (32–255)
Rifampin, isoniazid and ethambutol	125 (31)	90 (34–143)	123 (45–262)
Rifapentin and isoniazid	48 (12)	91 (34–137)	86 (30–243)
Rifapentin, isoniazid and ethambutol	32 (8)	101 (66–146)	156 (54–266)
Isoniazid and ethambutol	10 (3)	108 (69–156)	191 (110–265)
Others	21 (5)	180 (51–263)	213 (105–547)
All regimens	399 (100)	89 (33–138)	111 (35–261)

IQR: interquartile range; NA: not applicable.
[a] Based on dispensary-reported unit cost of each drug.

Table 4. Frequency of examinations and their associated costs during period of extended TB treatment in patients seen at Chang Ping TB dispensary, Beijng, China, 2008–2009

Examinations	Patients n (%)	Median no. of times examination repeated (IQR)	Median examination cost[a] per patient (IQR)
Chest fluoroscopy	0 (0)	NA	NA
Chest radiograph	250 (63)	2 (1–3)	10 (5–15)
Computed tomography	17 (4)	1 (1–1)	94 (94–94)
Routine blood test	272 (68)	2 (1–4)	7 (3–12)
Routine urine test	250 (63)	2 (1–3)	3 (1–4)
Liver and renal function test	274 (69)	2 (1–3)	12 (6–20)
Smear	18 (5)	2 (1–3)	5 (2–7)
Culture	6 (2)	2 (2–2)	20 (20–20)
Others	48 (12)	1 (1–2)	NA
All examinations	287 (72)	8 (4–13)	32 (16–54)

IQR: interquartile range.
[a] US$, based on dispensary-reported unit cost of each examination.

In comparing the two groups of patients, those who received extended treatment had a higher prevalence of smear-positive pulmonary disease with higher sputum smear grades, more frequent association with extrapulmonary disease (especially pleurisy), more cavities and more lobes affected with radiographic abnormalities. In short, they had clinical, microbiological and radiographical evidence of more severe disease that the clinician may have wished to treat for longer in order to improve individual prognosis and to ensure more certain cure and thus prevent further transmission of TB in the community.

In the present study, the frequency of recurrent TB was similar in both groups, i.e., extended treatment was not associated with prevention of a second episode of TB. Recurrence of TB was determined by a retrospective search for matching names in different data bases; it is possible that we missed patients with recurrent disease and thus may have underestimated the frequency of this condition. However, the WHO standard 6-month treatment regimen, which is used in China, is associated with a recurrent TB rate of 0.5–3.3% within 3 years,[8–12] with most recurrences occurring within 1 year,[13] which is reassuringly similar to our findings. A prospective study in Bangladesh compared patients who remained smear positive after finishing the intensive phase and then prolonged treatment for 1 month to those who did not prolong the intensive phase, and showed that prolonged treatment decreased the rate of relapse within 2 years from 3.3% to 1.4%.[14] However, that study was confined to patients who remained smear positive. In our study, the extended treatment was performed on patients who were smear negative and reported to be cured or to have completed treatment. In a country such as China, with a low prevalence of HIV in the general population,[15] we doubt that a 2–3 month period of extended treatment will have a significant effect on further lowering the rate of TB recurrence.[10]

The additional costs of extended treatment were substantial, given that one-third of the patients were peasants. A previous study in four provinces of China showed that, in 2006, TB would cost every peasant patient ¥1240–2600 (about US$203–424), representing 12.6–39.9% of their annual family income and NTP paid about 20% of them.[16] In our study the length of extended treatment varied according to the type of drugs administered, and the costs varied from US$85 to almost US$200. Furthermore, many patients were subjected to repeat chest radiographs and urine and blood tests that included liver and renal function tests at a median cost of around US$30. These were the direct costs that a patient had to pay for anti-TB drugs and for laboratory and radiographic examinations; they did not include indirect costs such as transport and time lost from work. These indirect costs were not measured, but other studies have shown that indirect costs might be 18–24% of direct costs.[17,18] Our analysis suggests that the economic burden of extended treatment on each patient was high.

The strengths of this study were the large number of patients assessed and the fact that the dispensary we selected was a typical basic DOTS unit of the China NTP. As such we feel that our findings are representative of clinical practice in other centres and in other counties in China. Limitations relate to the operational nature of the study, the fact that this was a retrospective record review and the concerns mentioned earlier about recurrent TB. We also have no information for patients with recurrent TB on culture and drug sensitivity patterns, and, therefore, cannot report on levels of drug resistance. And we could not determine whether the recurrent TB was caused by endogenous reactivation or exogenous re-infection. In the individual patient such determination requires collection of *Mycobacterium tuberculosis* isolates during the initial and subsequent episodes of TB for spoligotyping, a rapid, PCR-based method of genotyping *M. tuberculosis* strains.

Where do we go from here? The results of this study show that there is no observable benefit from extended treatment in terms of preventing recurrent TB but that there is a considerable direct cost to the patient, who has to pay for an additional 2–3 months of anti-TB drugs and laboratory and radiographic investigations. Additional retrospective studies similar to the one we have conducted should be undertaken in other parts of China to validate our results and determine the widespread nature of this practice.

Our results, based on retrospective data and unmatched cohorts of patients, are unlikely to convince the advocates of extended treatment that it is probably not of benefit. This will probably need a prospective study with carefully matched cohorts of patients who are assessed for adverse effects of drugs and followed actively with sputum smears and cultures at set time intervals. Such a study will be costly, but given the possibility that extending TB treatment is a widespread practice in China, the findings would be of benefit to patients with TB and to the whole NTP.

In conclusion, just over 40% (399/935) of pulmonary TB patients in a single DOTS dispensary in Beijing, China, received extended treatment for several months after being declared successfully treated with first-line anti-TB treatment. Extended treatment was given to those with more severe disease at presentation. Extended treatment was associated with high direct patient cost for drugs and laboratory/radiographic investigations, and there was no evidence that it reduced the risk of recurrent TB. Further well-designed cohort studies are warranted to convince the advocates of extended treatment of the probable lack of benefit of this intervention.

Authors' contributions: YYX, YL, LXW, XD and SMC conceived the study; YYX, ADH and SG designed the study protocol; YYX, XD, ZGZ, TJG and SMC participated in the conduct of the study; YYX, XD, ADH and SG analyzed and interpreted these data. YYX, ADH and SG drafted the manuscript; LXW, XD, SMC and YL critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. XD and LXW are guarantors of the paper.

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